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Review article

Pharmacological, neural, and psychological mechanisms underlying psychedelics: A critical review

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ABSTRACT

This paper provides a critical review of several possible mechanisms at different levels of analysis underlying the effects and therapeutic potential of psychedelics. At the (1) biochemical level, psychedelics primarily affect the 5-HT_{2A} receptor, increase neuroplasticity, offer a critical period for social reward learning, and have anti-inflammatory properties. At the (2) neural level, psychedelics have been associated with reduced efficacy of thalamo-cortical filtering, the loosening of top-down predictive signaling and an increased sensitivity to bottom-up prediction errors, and activation of the claustro-cortical-circuit. At the (3) psychological level, psychedelics have been shown to induce altered and affective states, they affect cognition, induce belief change, exert social effects, and can result in lasting changes in behavior. We outline the potential for a unifying account of the mechanisms underlying psychedelics and contrast this with a model of pluralistic causation. Ultimately, a better understanding of the specific mechanisms underlying the effects of psychedelics could allow for a more targeted therapeutic approach. We highlight current challenges for psychedelic research and provide a research agenda to foster insight in the causal-mechanistic pathways underlying the efficacy of psychedelic research and therapy.

1. Introduction

Psychedelic drugs are a kind of psychoactive substance that produce substantial alterations to perception, cognition, and emotion. So-called classic psychedelics, such as LSD and psilocybin, are defined by their serotonergic mechanism of action (for this reason they are sometimes referred to as "serotonergic psychedelics"; cf., Nichols, 2016). Historically, psychedelics have been used in ritual and religious contexts across several cultures for hundreds of years (Schultes, 1969).

Recently, there has been a trend of increasing recreational use of psychedelics in Europe and the US, as evidenced for instance by the European Drug Monitor (European Drug Report: Trends and Developments, 2019) and the Global Drug Survey (Winstock et al., 2018). LSD or psilocybin microdosing (ingesting small, sub-subjective, doses) is on the rise (Cameron et al., 2020). Furthermore, many people participate in psychedelic retreats involving large doses of psychedelics, especially involving psilocybin or ayahuasca, which typically last several days and are organized in ritual or meditative settings (e.g., Smigielski, Kometer et al., 2019).

We are also currently witnessing a psychedelic revival in scientific and clinical research Psychedelics are increasingly being studied in clinical studies (Carhart-Harris et al., 2014; Carhart-Harris, Muthukumaraswamy et al., 2016; Griffiths et al., 2006). Based on data from preliminary clinical trials, psychedelics appear to have a strong therapeutic potential for the treatment of several psychiatric disorders, including severe depression (Carhart-Harris, Bolstridge et al., 2016; Carhart-Harris et al., 2021; Davis et al., 2020), addiction (Bogenschutz et al., 2015; Johnson et al., 2017), obsessive-compulsive disorder (Moreno et al., 2006), anxiety related to a life-threatening medical diagnosis (Griffiths et al., 2016; Ross et al., 2016), post-traumatic stress disorder and cancer-related anxiety disorders (Krebs and Johansen, 2012; Kyzar et al., 2017; Rucker et al., 2018). In sum, there is a 'psychedelic renaissance' and widespread optimism regarding the potential therapeutic effects of psychedelics (Sessa, 2018) coupled with calls for caution (Yaden et al., 2021).

In the extant literature, several different explanations have been offered as to how psychedelics could exert their therapeutic effects. Some have pointed out the potential of psychedelics to occasion mystical-like or self-transcendent experiences, which many people consider to be among the most meaningful in their lives (Griffiths et al.,

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2006). Others have suggested that psychedelics loosen our prior beliefs, thereby opening a window of opportunity for adopting more positive beliefs and evaluations (Carhart-Harris and Friston, 2019). But at the same time, psychedelics also induce a number of other more biologically basic effects including an increase in brain-derived neurotrophic factor (BDN), which in turn stimulates neuroplasticity (Vollenweider and Preller, 2020). However, the primary causal mechanisms remain poorly specified and a large amount of uncertainty remains. An integrative perspective on how these different explanations are related is lacking, as different authors have tended to emphasize or focus selectively on one or another explanatory mechanism.

In this paper, we organize a review of psychedelics in terms of levels of analysis, thereby providing an integrative overview of the state of the evidence regarding the different potential mechanisms of action of psychedelics (see Fig. 1). We will outline the different explanations that have been offered for the action of psychedelics at the (1) pharmacological level, (2) the neural level and (3) the psychological level. Following the specification of these mechanisms, we will discuss the relationship between these different levels of analysis. We conclude by highlighting current challenges for psychedelic research and present a roadmap to elucidate the relative contribution of the different causal mechanisms underlying the psychedelic experience.

Of course, our model could be extended to include social, contextual, and cultural levels of analysis as well. The central importance of 'set' (i.e., the beliefs, expectations, and current mindset that people bring to a psychedelic experience) and 'setting' (i.e., the current environment and broader socio-historical context) for the psychedelic experience was already acknowledged in the 1960 s. Also in other fields the so-called bio-psycho-social model acknowledges the importance for extra-pharmacological factors in the effects of different types of psychoactive substances (Engel, 1977). Systematic research on the role of set and setting on the psychedelic experience is scarce (however, for an overview of research on set & setting in the use of ayahuasca, see, e.g.,: Hartogsohn, 2021). In our review we therefore limit ourselves to discussing contemporary research on the pharmacological, neural, and psychological mechanisms involved in psychedelics. But we return to the important topic of culture and context in the final section.

2. Pharmacological mechanisms

Classic psychedelics typically refer to serotonergic hallucinogenic substances, such as lysergic acid diethylamide (LSD), psilocybin (the psychoactive compound in magic truffles and mushrooms), and N,N-Dimethyltryptamine (DMT). These drugs have a common mechanism of action, consisting of partial agonism for the serotonin 5-HT_{2A} G protein-couple receptors (GPCRs; cf., Kim et al., 2020). The basic molecular structure of the classic psychedelics resembles the serotonin molecule (Nichols, 2016). Early research from the 50′s and 60′s of the last century has shown that the repeated administration of LSD and psilocybin induces cross-tolerance, whereby the efficacy of the drugs decreases after repeated dosages (Nichols, 2004). In humans, 5-HT_{2a} receptor occupancy also correlated with the subjective effects of psychedelics (Madsen et al., 2019).

Administration of ketanserin, which is a 5-HT_{2A} antagonist, prevents the typical subjective effects associated with psychedelics, such as synesthesia and sensory alterations, to occur (Holze et al., 2021; Vollenweider et al., 1998). Animal studies have indicated a role of the 5-HT_{2A} receptor in the action of psychedelics as well: a reliable indicator of the psychedelic state in rats and mice is the so-called head-twitch response, whereby the animal repeatedly and rapidly shakes its head (Halberstadt and Geyer, 2011). Genetically mutated mice that don't have a functioning 5-HT_{2a} receptor, also do not show the head-twitch response under the influence of psychedelics, indicating that this receptor sub-type is a crucial mechanism of action for psychedelics.

Through psychedelics' partial agonism of the 5-HT_{2A} receptor, cortical layer 5 pyramidal neurons show an increased frequency of spontaneous and evoked excitatory post-synaptic currents and potentials (Aghajanian and Marek, 1999) and increase their firing rate upon activation (Marek and Schoepp, 2021; for an overview of the effects, see Fig. 2). The 5-HT_{2A} receptor is involved in learning and memory, pain perception, and the sleeping/waking cycle (Duerler et al., 2022). 5-HT_{2A} receptors can be found in the so-called pyramidal neurons in layer 5 of the neo-cortex, in the thalamus, and in the reticular nucleus, which are involved in visual perception and attention (Vollenweider and Preller, 2020). A high concentration of 5-HT_{2A} receptors can also be found in so-called higher-order association areas in the brain, such as the temporo-parietal junction and the medial prefrontal cortex (cf., Beliveau et al., 2017), which could explain why psychedelics affect so many cognitive, perceptual, and emotional functions. However, using a different method to map 5-HT_{2A} -receptor density, the strongest concentration of receptors was found in the striate and extrastriate visual cortex (Preller et al., 2018), which in turn could explain the prevalent

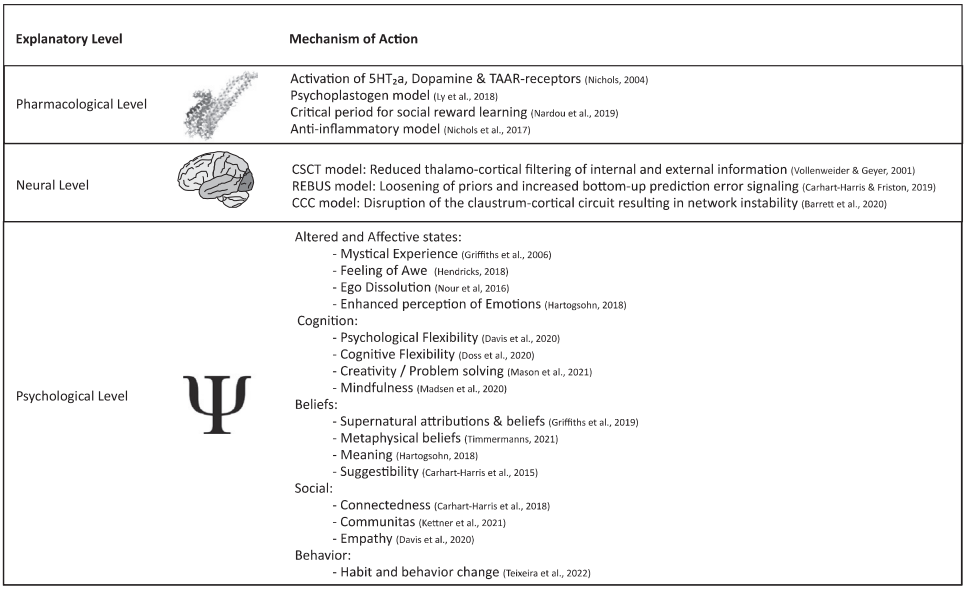

Fig. 1. Different levels of analysis that specify the pharmacological (upper panel), neural (middle) and psychological (lower panel) mechanisms through which psychedelics exert their effects. Key mechanisms and relevant references to each of these mechanisms are listed and are extensively discussed in the main text.

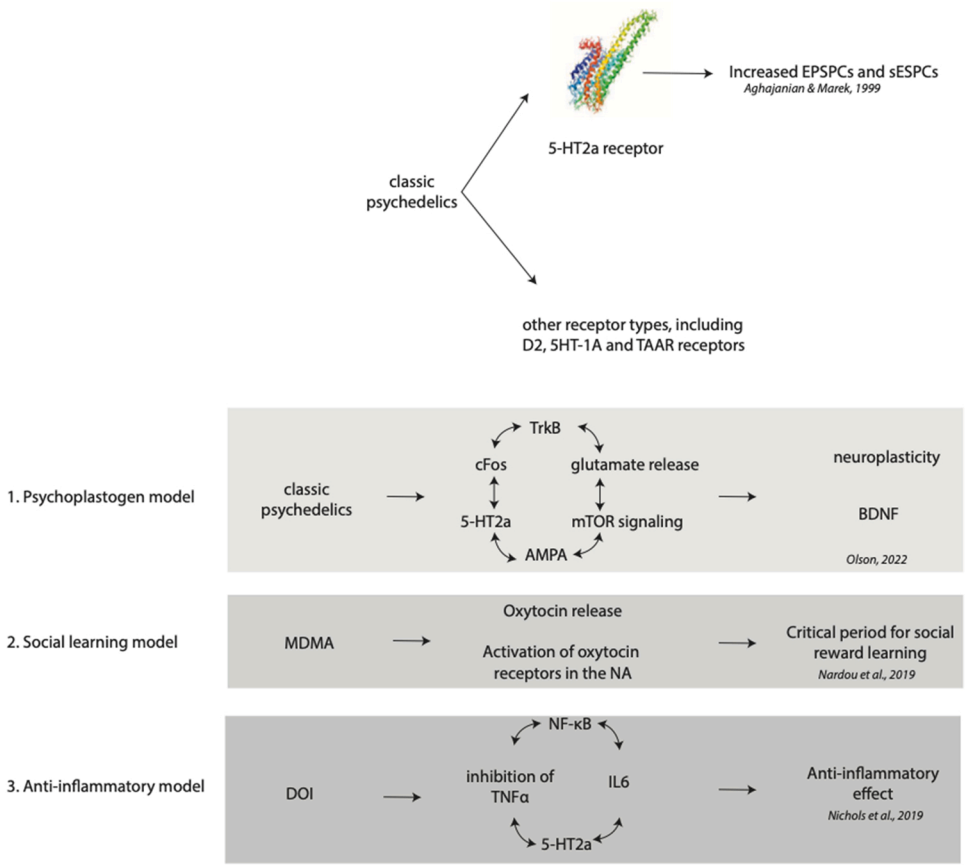

Fig. 2. : Simplified model of the neurochemical effects of psychedelics, according to the (1) psychoplastogen model, the (2) social learning model and the (3) anti-inflammatory model. Abbreviations stand for: EPSPC = excitatory postsynaptic current; sESPCs = spontaneous excitatory postsynaptic currents; 5-HT_{2A} = 5-HT_{2A} serotonin receptor; TrkB = Tropomyosin receptor kinase B; mTOR = mammalian target of rapamycin; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; cFos = protein C-Fos; BDNF = brain-derived neurotrophic factor. NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells; IL6 = Interleukin 6; TNFα = tumor necrosis factor alpha.

visual hallucinations that appear a recurring feature of classic psychedelics (Carhart-Harris and Friston, 2019).

Recent findings, however, somewhat complicate the view that 5-HT_{2A} receptor is the primary therapeutic mechanism at the pharmacological level and point to potential limitations. Hesselgrave et al. (2021) found that assays of hedonic behavior that were assessed after psilocybin administration were *not* impacted by the 5-HT_{2A} antagonist ketanserin. In addition, blocking of the 5-HT_{2A} receptor in mice abolished the head-twitch response, but did not block the induced changes in structural plasticity (Shao et al., 2021). These findings suggest that the therapeutic impact of psilocybin may be conveyed through other pharmacological mechanisms. Additional pre-clinical rodent studies and human trials will be necessary to assess the robustness of 5-HT_{2a} antagonism using ketanserin (and other means) and thus arrive at a more complete understanding of the role of 5-HT_{2a} agonism.

In addition, next to the affinity with the 5-HT_{2A} receptor, classic psychedelics (and in particular LSD) also bind to other receptors, including many different sub-types of the serotonin and dopamine receptors (Halberstadt and Geyer, 2011). For instance, pre-treatment with the 5-HT_{1AR} agonist buspirone resulted in reduced elementary and complex visual hallucinations, suggesting a modulatory effect of the 5-HT_{1AR} receptors on the 5-HT_{2A} receptor mechanisms (Pokorny et al., 2016). Blocking of the D2 dopamine receptor with haloperidol instead reduced the effects of psilocybin on positive derealization, while having no effect on visual hallucinations or working memory (Vollenweider et al., 1998).

LSD has been characterized by a phased response, whereby during the first phase primarily the 5-HT_{2A} receptor is activated, while after 90 min the D2 receptor is activated as well (Marona-Lewicka and Nichols, 2007). Currently no study has directly evaluated the effect of blocking dopamine receptors on the subjective effects of LSD. Despite their different pharmacological profile and affinity for different receptor sub-types, recent evidence indicates that the subjective effects of 30 mg psilocybin and 100 or 200 mg of LSD were statistically indistinguishable (Holze et al., 2022), thereby calling into question the potential for establishing a precise relationship between activation of different receptor sub-types and phenomenological features.

Another receptor potentially involved in the therapeutic effects of psychedelics is the trace amine-associated receptor (TAAR). Psychedelics activate the TAAR1 receptor, which in turn exerts an inhibitory effect on dopaminergic activity (De Gregorio et al., 2016). These receptor-mechanisms may underlie the therapeutic effects of psychedelics on addiction and depression by affecting the sensitivity to reward and stress at a pharmacological level (Kyzar et al., 2017).

Next to exerting effects through activation of the 5-HT_{2A} receptor, psychedelics also induce a cascade of other pharmacological processes. Below we will elaborate on three different mechanisms that have been described in the literature, including (1) the psychoplastogen model, (2) the critical period for social reward learning model and (3) the anti-inflammatory model (for an overview, see Fig. 2).

2.1. Psychoplastogen model

At a neural level it has been found that classic psychedelics such as LSD and DMT increase synaptic growth and increase the complexity of the dendrites and the number of synapses, thereby increasing the number of connections between neurons (Ly et al., 2018). The explanatory mechanism for this increased neuroplasticity can be found in the post-synaptic effects of classic psychedelics in layer 5 of the medial prefrontal cortex, where they induce a burst of glutamate release (Vollenweider & Kometer, 2010) and sustained α-amino-3--hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) activation. This in turn triggers the release of brain-derived neurotrophic factor-tropomyosin receptor kinase B (BDNF-TrkB), and

mammalian target of rapamycin (mTOR) signaling, which in turn upregulate the expression of neuroplasticity related genes and the synthesis of proteins of synaptic components via eukaryotic elongation factor 2 (eEF2; for review, see: Aleksandrova and Phillips, 2021). The acute administration of psychedelics also increase the expression of different genes that encode for the synthesis of a variety of proteins, that foster neuroplasticity and learning (Nichols and Sanders-Bush, 2002).

Taken together, these effects result in an amplification of neuroplasticity, which might well have a therapeutic effect by fostering adaptive rewiring of neural circuits. Indirect evidence for the potential beneficial neuroplastic effects of psychedelics can be found in the observation that depressive patients are characterized by chronically lower levels of BDNF (Baumeister et al., 2014). More direct evidence from animal studies indicates that psychedelic-induced neuroplasticity can increase prosocial behavior (De Gregorio et al., 2021) and reverse stress-induced anxious behavior (De Gregorio et al., 2022). However, it remains to be established to what extent these neuroplastic effects eventually are also beneficial in humans. Only one study has established a relationship between ayahuasca-induced increases in BDNF levels and symptom improvement in depression (de Almeida et al., 2019). Recent studies indicate that only a high dose of LSD (200 mg) resulted in a statistically significant increase in BDNF levels, whereas lower doses or blocking of the 5-HT_{2A} receptor did not (Holze et al., 2021; Holze et al., 2020). In contrast, another study found that microdoses of LSD between 5 and 20 mg did increase BDNF levels (Hutten et al., 2021). Thus, more research is needed to establish the robustness of psychedelic-induced changes in BDNF and the downstream effects on neural plasticity (e.g., by using imaging techniques to measure white-matter tractography such as diffusion tensor imaging; cf., Le Bihan et al., 2001).

Based on the observations of increased synaptic growth and density of neurons, a model of the therapeutic effects of psychedelics has emerged that emphasizes these effects. According to this view, psychedelics could be considered "psychoplastogens" (e.g., Olson, 2018), or substances capable of promoting rapid neural plasticity both structurally and functionally. Substances have been engineered that create psychoplastogenic effects without the altered state of consciousness associated with classic psychedelics (e.g., Cameron et al., 2021). Microdosing, i.e., the regular use of sub-hallucinogenic doses of psychedelics, is another trend that fits well with the psychoplastogen model (Ona and Bouso, 2020) and people microdose for a variety of different reasons, including cognitive enhancement, depression and anxiety (Kuypers et al., 2019). However, the actual efficacy of psychedelic microdosing has been a topic of ongoing debate and currently the preponderance of evidence highlights the central role of placebo- and expectancy-effects accounting for most of the effects observed in the literature (Szigeti et al., 2021). Furthermore, while it appears quite likely that neural plasticity from psychedelics plays some role in the mechanisms that convey the therapeutic effects of psychedelics, the psychoplastogen model is limited by its lack of specificity. There is a wide array of manipulations – environmental, social, and pharmacological – that promote neuroplasticity, so psychedelics may not be special in this regard (see for instance: Galliano et al., 2021). Here, as elsewhere in this review, the proposed mechanism may not be sufficiently specific to psychedelic action to account for all the effects that psychedelics exert.

2.2. Critical period for social reward learning

Classic psychedelics like LSD and 2,5-Dimethoxy-4-iodoamphetamine (DOI) increase levels of oxytocin, as does MDMA (3,4-Methyl enedioxy methamphetamine), a psychoactive substance with a similar time course of acute subjective effects as classic psychedelics but distinct pharmacological and phenomenological properties (Nardou et al., 2019; Thompson et al., 2007). Oxytocin is a hormone that results in strong feelings of empathy, connectedness, and sociability (Schindler et al., 2018). Oxytocin often increases trust, willingness to cooperate, and prosocial tendencies (De Dreu, 2012), though possibly only for in-group members (De Dreu and Kret, 2016). Thus, some of the acute subjective effects experienced during a psychedelic experience might be caused by the increased oxytocin levels induced by psychedelics. However, other studies have shown that MDMA but *not* an intranasal oxytocin administration induced strong pro-social and emotional effects (Kirkpatrick et al., 2014), that plasma oxytocin levels were more strongly increased following the administration of MDMA compared to intranasal oxytocin (Kirkpatrick et al., 2014), and that oxytocin did not mediate MDMA-induced enhancement of emotional empathy (Kuypers et al., 2014). While care must be taken in extrapolating from MDMA research to classic psychedelics, these findings suggest that biochemical mechanisms including but certainly not limited to oxytocin may contribute to the prosocial effects of classic psychedelics.

Another mechanism could be the opening of a critical period in social reward learning, which has been observed in rodents. Rodents (and humans as well as other mammals) are highly sensitive to social cues related to reward during adolescence but far less sensitive as maturation occurs. Re-opening the critical window for social reward learning may allow social manipulations that occur during this period to propagate longer term beneficial effects (Nardou et al., 2019). This re-opening of the critical period for social reward learning appears to occur in MDMA through binding to the serotonin transporter which then results in oxytocin release. Again, care must be taken when generalizing from MDMA to classic psychedelics, but preliminary evidence has shown that this is also the case in rodents given psilocybin (Dolen, personal communication). This model is more specific and well-characterized than the much broader psychoplastogen view. However, it may not be able to account for the more acute anti-depressant effects that have frequently been observed, as these occur before a period of social learning can occur. Overall, the critical period for social reward learning may be an important mechanism but may not offer a complete account of the therapeutic mechanisms.

2.3. Anti-inflammatory model

Classic psychedelics have an effect at the genetic level as well. They affect genetic transcription through the activation of a relatively small percentage of 5-HT_{2A} receptors (Nichols et al., 2017). These so-called 'trigger neurons' in turn activate an anti-inflammatory mechanism, thereby providing a potential application of psychedelics for other neurological disorders, such as Alzheimer's disease and Parkinson (Kyzar e.a, 2017). These diseases are characterized by a chronically over-active immune system and psychedelics could potentially remedy these diseases through their anti-inflammatory properties. The anti-inflammatory mechanism of psychedelics could also play a protective role in depression and addiction (Flanagan & Nichols 2018). Psychedelics have an inhibitory effect on cytokines, such as tumor necrosis factor (TNF) and interleukin (IL), that normally trigger the inflammatory response in the body. A disturbed functioning of TNF and IL has been associated with depression and anxiety-related disorders (Wichers and Maes, 2002). The anti-inflammatory mechanisms of psychedelics could potentially help to explain why the improvements, e.g., in depression and anxiety, already occur after a single session with a classic psychedelic (Flanagan & Nichols 2018). This model is limited by its lack of specificity. If the therapeutic impact of psychedelics was almost entirely due to the anti-inflammatory properties, one might expect other potent anti-inflammatory agents to have nearly equivalent therapeutic effects, but this does not appear to be the case.

Summary In short, psychedelics exert different effects at the pharmacological level: in addition to stimulating the $5HT_{2A}$ receptor (and other serotonin sub-receptors), classic psychedelics increase levels of glutamate and oxytocin, the production of BDNF, neurogenesis, and have an anti-inflammatory effect. It could well be the combination of these different effects explains why psychedelics can be effective for a wide range of different disorders, ranging from depression to addiction. We note that each of these findings should be considered somewhat

preliminary before replications are conducted. Furthermore, each of the models reviewed emphasize pharmacological processes that are rather broad and often non-specific to psychedelic substances so none can be considered complete explanations at this point.

3. Neurocognitive mechanisms

In the scientific literature there are a number of different and often complementary neuroscientific explanations that have been proposed to account for the effects of psychedelics at a brain-level (see Fig. 1). Here we will provide a brief overview of the three most prominent explanations, namely (1) the thalamo-cortical filter theory, (2) the relaxed beliefs under psychedelics (REBUS) model, and (3) the claustro-cortical circuit model (CCC) model.

Before presenting these different neural models, we briefly discuss the effects of psychedelics on cognitive and attentional processing, as these effects constrain the list of desiderata for a neuroscientific theory of psychedelics (the acute subjective effects of psychedelics will be discussed in the section 'psychological mechanisms'). Several studies have shown that psilocybin has an attention-disrupting effect, where performance on basic attentional paradigms (e.g., such as the inhibition of return) is strongly impaired (Carter et al., 2005a; Daumann et al., 2008; Gouzoulis-Mayfrank et al., 2006), and this effect is likely mediated by the 5-HT_{1A} receptor, as ketanserin did not prevent the psilocybin-disrupting effects on attention (Carter et al., 2005b). Psychedelics also impaired cognitive and executive control, as reflected for instance by a decreased prepulse inhibition (PPI), a stronger Stroop-interference effect (Quednow et al., 2012; Vollenweider et al., 2007), higher error rates in the Sternberg paradigm (Bouso et al., 2013), and impaired performance on a go/no-go task (Schmidt et al., 2018). Working memory is also negatively affected by psychedelics, as evidenced by studies using standard neuropsychological assessments (Barrett et al., 2018) as well as a temporal reproduction task (Wittmann et al., 2007). Finally, despite anecdotal evidence that psychedelics increase fluency in skilled tasks (e.g., juggling or music making), the evidence points towards psychedelic-induced impaired motor performance (Barrett et al., 2018; Carbonaro et al., 2018). Thus, overall, psychedelics appear to have a detrimental effect on cognitive and attentional processing. The different neural theories discussed in this section each provide clues as to why this might be the case.

3.1. The cortico-striato-thalamo-cortical (CSTC) theory

An early account of the neurocognitive mechanisms of psychedelics builds on the idea that psychedelics act by releasing sensory filters. The so-called cortico-striato-thalamo-cortical (CSTC) model proposes that our brain normally functions through feedback loops between cortical regions and different thalamic nuclei, including the medio-dorsal nucleus, the thalamic reticular nucleus, and the ventral striatum (Vollenweider and Geyer, 2001). These feedback loops provide a mechanism to prevent an overload of sensory and interoceptive information. The thalamic nuclei work as a filter mechanism, to control the amount of interoceptive signals related to the body and exteroceptive signals related to external sensory information that are projected to higher-level cortical regions. The filtering function of the thalamus is controlled by the prefrontal cortex, which acts as a selective gating mechanism. Psychedelics tend to release this inhibitory control mechanism, meaning that the prefrontal cortex has a reduced inhibitory control over the thalamic reticular nucleus, thereby resulting in an overload of information sent to other sensory brain regions (Vollenweider and Preller, 2020).

The reduced gating of the thalamus has been associated with different neural mechanisms, including excessive stimulation of the 5-HT_{2A} receptors, blockade of NMDA receptors and increases in dopaminergic and GABAergic projections (Geyer and Vollenweider, 2008). In support of the CSTC model, early PET-studies and more recent fMRI studies have shown that psychedelics result in an altered activation and connectivity of the prefrontal cortex and the thalamus, which in turn were associated with subjective changes in the experience of the participants (Preller et al., 2019; Vollenweider et al., 1997). According to the CSTC model, the psychedelic experience shows similarities with the psychotic state, lending support to the so-called psychotomimetic model of psychedelics. The psychotomimetic hypothesis suggests that psychedelic experiences provide a transient working model of psychosis. The psychotomimetic view has been largely refuted (discussed further below), but the psychedelic and psychotic states may indeed both be characterized by 'gating deficits', resulting in an overload of sensory information and, potentially, an altered perception of the self and reality (Vollenweider and Geyer, 2001). In support of this model, enhanced connectivity of the thalamus with other brain regions has been observed to correlate with the subjective effects of LSD (Muller et al., 2021). The CSTC model also fits well with the attentional impairments that have been associated with psychedelics, as the gating function of the thalamus is disrupted, bearing similarities to the psychotic state that is also associated with altered thalamic connectivity and impaired attention (Anticevic et al., 2015).

However, increased metabolic activity of the thalamus has only intermittently been observed during acute psychedelic effects (Gouzoulis-Mayfrank et al., 1999; Vollenweider et al., 1997). The CSTC model also has its limitations, as behavioral proxies of reduced thalamic gating, such as the pre-pulse inhibition and the inhibition of return have shown only mixed results under the acute effect of psychedelics (Gouzoulis-Mayfrank et al., 2006, 1998; Vollenweider et al., 2007). Moreover, the CSTC model may need to be extended to include efference-based signaling from layer V pyramidal neurons to higher-order thalamic nuclei (Sherman, 2016). In sum, the CSTC model provides a plausible account for some of the neural and phenomenological effects observed under psychedelics, including an intensification of sensory processing bearing similarities to the psychotic state.

3.2. The relaxed beliefs under psychedelics (REBUS) model

An integrative account for the effects of psychedelics can be found in the REBUS model, which integrates the so-called entropic brain hypothesis with the free-energy principle (Carhart-Harris and Friston, 2019). A basic premise of this framework is that under normal circumstances of everyday consciousness, our brain functions like a prediction machine, continuously aiming to 'explain away' the incoming sensory input (Clark, 2013; Friston and Kiebel, 2009). That is, our subjective experience of the world is instantiated through a generative hierarchical model that yields predictions to anticipate the sensory input that enters our senses. Only in case of a mismatch between the sensory predictions and the actual input, a prediction error signal is generated, which in turn results in the updating of the generative model. Prediction-error signaling is modulated by the precision-weighting of the sensory signals, whereby more reliable signals are assigned a higher confidence in terms of belief updating. Psychedelics, through their action on the 5-HT_{2A} receptors, promote excessive excitability of deep-layer pyramidal neurons that encode the precision of beliefs. As a consequence, prediction errors fail to be suppressed. Thus, according to REBUS, psychedelics loosen prior predictions, while increasing sensitivity to bottom-up prediction error signaling (Carhart-Harris and Friston, 2019).

Low doses of psychedelics primarily induce perceptual effects, which may be related to the high density of 5-HT_{2A} receptors in the visual system (Preller et al., 2018). The effects of the loosening of prior beliefs on perception are exemplified for instance in the phenomenon of 'breathing walls', as our perception of a wall is no longer constrained by the prior that it represents a solid object. The absence of correct prediction error updating under psychedelics, also accounts for the well-known phenomenon of visual trails, that refers to the experience that moving objects such as birds or a moving hand seem to leave a visual 'trace' under the influence of psychedelics (Dubois and

VanRullen, 2011). In these cases, our brain fails to accurately update the visual representation of moving objects, thereby yielding the impression of an elongated object or 'trail'. Typically, the strongest visual effects under the influence of psychedelics are experienced when one's eyes are closed, in which case there is no visual sensory input that can be used to 'correct' one's internal models based on prediction-error signaling (Carhart-Harris and Friston, 2019).

At higher doses, more high-level regions of the cortical hierarchy are affected by psychedelics, resulting in altered perceptions of the self and changes in high-level beliefs. The Default Mode Network (DMN) consists of a set of strongly interrelated brain regions, such as the posterior cingulate cortex, the medial prefrontal cortex and the temporo-parietal junction, and has been implicated in task-free processing, such as mind-wandering, self-referential processing and daydreaming (cf., Raichle, 2015). The DMN is a key example of a 'high-level' region that may be at the top of the cortical hierarchy, being primarily involved in representing high-level aspects of the self (Letheby and Gerrans, 2017). fMRI studies have shown that during the psychedelic experience, there is a decreased activity in the DMN compared to baseline or placebo conditions (Carhart-Harris et al., 2012; Carhart-Harris, Muthukumaraswamy et al., 2016). Moreover, the strength of the decrease in DMN activity has been shown to be related to self-reported ego-dissolution. These findings indicate that changes in DMN under psychedelics could perhaps reflect the loosening of high-level beliefs and schemas (discussed below).

However, the observed decrease in DMN activity is in apparent contrast with the earlier studies showing an increased activity in prefrontal areas associated with the psychedelic experience (Vollenweider et al., 1997). These contrasting findings may be related to methodological differences between studies, perhaps especially in details regarding the statistical analyses that were conducted (e.g., whether the global blood volume was regressed out or not; for discussion, see: Carhart-Harris et al., 2017). The discrepancies could also emerge from the dynamic nature of the psychedelic experience itself, which may at points be characterized by a loss of self, and at other phases by a stronger attentional focus on sensory experiences instead. In any case, we suggest substantially qualifying any claims that the DMN constitutes one's "sense of self", which is how this model is sometimes portrayed in the media.

The REBUS model also integrates insights from the entropic brain hypothesis (Carhart-Harris, 2018), according to which during a psychedelic experience there is an increase in the connectivity between different brain networks that are normally not very strongly connected (Carhart-Harris et al., 2012; Carhart-Harris, Muthukumaraswamy et al., 2016, 2013). The notion of the 'entropic brain' refers to the idea that under the influence of psychedelics, our brain is in an increased state of disorder, or entropy, that differs strongly from our normal waking consciousness (Carhart-Harris et al., 2014). In support of this idea, a neuroimaging study found that brain-based measures of entropy did increase during the acute effects of psychedelics (Schartner et al., 2017). The increased entropic brain states observed under psychedelics help to explain, for instance, the synesthetic experiences that are typically reported under psychedelics: sounds may induce specific colors, touch may evoke specific sounds, etc. These synesthetic experiences could be a consequence of the increased cross-talk between different primary sensory brain regions, thereby enabling experiences that are beyond our everyday waking consciousness (Pink-Hashkes et al., 2017). Through the increase in connectivity, the predictability of the processing pathways in our brain decreases, thereby making it more unpredictable which specific processing route information will take. The increased entropy of the brain therefore may also account for the unpredictable effects of the psychedelic experience: in advance, it is difficult to predict which direction the experience will take. A comparison that is often made is with a skiing hill, whereby skiers typically take the beaten track to get down the hill. Under psychedelics, these beaten tracks are wiped out, thereby steering one along hills and roads not yet taken (Watts and Luoma, 2020). We also note that the REBUS model can account for the disruptive effects of psychedelics on attention, as on the predictive processing model attention can be conceived of as the precision of the prior expectations that are shaping our perception (Clark, 2016). Thus, loosening of prior predictions may tend to result in less precise predictions and impaired attentional processing.

The REBUS model potentially helps to account for the therapeutic efficacy of psychedelics. According to the REBUS model, disorders such as depression or obsessive-compulsive disorder are characterized by maladaptive hyperpriors, i.e., fixed and rigid beliefs that are resistant to change, such as an overly negative self-image or recurring compulsive thoughts (e.g., 'People don't like me, so I'd better avoid social situations'). These hyperpriors in turn exert a strong top-down effect on other beliefs, actions, and emotions. Maladaptive priors are resistant to change, because one of the key characteristics of depression is excessive rumination in a self-reinforcing pattern of thoughts and actions (e.g., 'I feel lonely and wouldn't know which friend to count on.'). According to the REBUS model, psychedelics result in the temporarily loosening of these maladaptive priors, by directly acting on the strength and the precision through which these prior beliefs are coded in the brain. As a consequence, people will become more open to new beliefs and insights that may be offered in a therapeutic context, not only at the time of the psychedelic experience, but also in the subsequent weeks and months. Next to the loosening of prior beliefs, psychedelics also directly offer a new embodied experience of connectedness and self-transcendence, which can challenge one's prior beliefs (e.g., 'I am lonely, but right now I feel a strong connection to everyone I know'). As such, the psychedelic experience could also induce a strong prediction error that runs counter to many prior beliefs resulting in a revision of one's mental schemes.

While the REBUS model has been influential in the field of psychedelic research as a potential unifying framework, it has also been criticized based on both conceptual and methodological concerns. At a conceptual level, it has been pointed out that the notion of entropy is not well defined (i.e., different researchers have used different measures), that it is unclear how low- and high-level regions in the brain should be defined and demarcated and that next to loosening prior beliefs, psychedelics (especially at lower doses) could also strengthen prior beliefs (Safron, 2020). At a methodological level, the studies on which the entropic brain theory and REBUS model were based suffer from small sample sizes and latitude for controversial analytical choices that may affect the results (cf., Preller et al., 2018). Also, whereas REBUS suggests increased prediction error signaling under psychedelics, other studies, however, have not found increases in surprise or other prediction errors during the acute effects of psychedelics (Schmidt et al.; Vollenweider and Preller, 2020).

In addition, the effects of psychedelics on the DMN appear to be too generic to provide a sufficiently specific account, as other substances (including SSRIs and MDMA) also result in an altered connectivity of the DMN (Muller et al., 2021). Finally, next to its effects on the DMN, psychedelics tend to result in even stronger changes in neural activity of other networks, including the task-positive network and the salience network (Lebedev et al., 2016; Mason et al., 2020). Thus, at present, the REBUS model appears more like a hypothesis than a well-established model. Additional confirmatory research with a high standard of methodological rigor is needed to test the predictions from the REBUS model.

3.3. The claustro-cortical circuit (CCC)

Another model of the neural mechanisms of psychedelics is the claustro-cortical-circuit (CCC) model (Doss et al., 2022), which is largely based on neuroimaging observations. The claustrum, a small subcortical gray matter which is located between the insula and the putamen, is highly saturated with 5-HT_{2A} receptors and has a large number of connections to various cortical and sub-cortical regions (Mathur, 2014; Nichols, 2016; Nichols et al., 2017). Claustrum involvement has been

noted in tasks related to cognitive control and sensory conflict (Atlan et al., 2018; Krimmel et al., 2019; White and Mathur, 2018). The claustrum is proposed to support cortical network states, which has been shown by the observation that direct activation of the claustrum through optogenetic imaging results in widespread cortical activation (Narikiyo et al., 2020). Activity of the claustrum in turn, is primarily driven by inputs from the prefrontal cortex (White et al., 2017), thereby establishing a recurrent claustro-cortical circuit.

Psychedelics, through the direct activation of 5-HT_{2A} neurons in the claustrum, may cause a destabilization of canonical brain network states (Nichols et al., 2017) and a decoupling between prefrontal areas and the claustrum (for a detailed account, see Doss et al., 2022). Doss et al. (2022) suggest that coordination between cortical regions and the claustrum is important for establishing cognitive control – and that psychedelics appear to disrupt this coordination, thus reducing cognitive control. In support of the CCC model, psilocybin has been shown to substantially alter networks related to cognitive control and claustrum functioning (Barrett et al., 2020). Specifically, psilocybin resulted in decreased activity of the claustrum which correlated with the experience of ineffability and a decreased coupling between the claustrum and other cortical networks. Given the involvement of the claustrum in cognitive control (Krimmel et al., 2019), the effects of psychedelics on the claustrum may also underlie the general decrease in executive functioning that is observed under the acute influence of psychedelics (e.g., LSD, Barret, Carbonaro et al., 2018; Schmidt et al., 2018).

While the CCC model appears to be a promising theory that potentially accounts for some of the widespread effects of psychedelics on different brain networks, the theory is currently underspecified, e.g., with respect to how and which specific canonical circuits are affected through psychedelic-induced changes in the claustrum (though it was found the claustrum interacted with both sensory and "higher level" multimodal networks). Moreover, as the claustrum is a relatively small brain structure, more advanced imaging techniques, including higher field fMRI, will be necessary to more clearly elucidate the flow of information between the claustrum and other brain regions. Finally, the acute subjective effects of psychedelics are highly variable, yet certain phenomenal features also seem to be reliably produced, as evidenced by several psychometric self-report measures that display orderly dose effects (Griffiths et al., 2011). It is unclear how reduced cognitive control alone could account for convergences on some self-reported acute subjective effects. The CCC model builds on and synthesizes several scientific observations; however, highly generalized brain network instability of the kind described by the CCC model does not seem to consist of a sufficient explanation for all of the acute subjective effects of psychedelics.

Summary In sum, three prominent theoretical frameworks have been proposed in the literature to account for the psychedelic experience, involving: (1) filtering mechanisms, (2) relaxed beliefs under psychedelics and (3) the claustrum-cortical circuit. We note that these models are not necessarily mutually exclusive accounts. For instance, according to the CCC model, disruption of network states could involve inhibition of sensory gating (as specified by the CSCT model), a relaxation of predictive signals (following the REBUS model) or disengagement of executive control networks. These theories are also directly related to the experiential psychological effects that have been associated with the psychedelic experience.

4. Psychological mechanisms

Psychedelics are often reported to induce a complex, dynamic, and multifaceted experience that is difficult to concisely convey. Below we detail some of the most prominent psychological effects that have been associated with the acute subjective effects of psychedelics, including (1) Altered and affective states, (2) changes in cognition, (3) belief change, (4) social effects, and (5) behavior change. We also outline some explanations that have been offered for each of these effects, as well as the therapeutic implications.

4.1. Altered and affective states

One of the key characteristics of psychedelics is their potential to induce an altered state of consciousness, including mystical experiences, feelings of awe, ego dissolution, and an enhanced perception of emotions. *Mystical-type experiences* are characterized by feelings of unity, transcendence of space and time, a noetic quality, ineffability, paradox, and sacredness, as well as positive feelings of bliss, joy, wonder and awe (Pahnke and Richards, 1969). The concept of mystical experience as it is used in contemporary psychedelic research dates back to William James's use of the term in his *The Varieties of Religious Experience* (1902), which was explicitly defined as a mental state – not to mean anti-rationalism nor supernaturalism (Yaden, Haidt, Hood Jr, Vago, and Newberg, 2017). The most common measure of mystical experience in the context of psychedelic research is the mystical experience questionnaire (MEQ; Barrett et al., 2015). Many people consider psychedelic-induced experiences to be among the most meaningful of their lives (Griffiths et al., 2006), even up to 30 years following the original experience (Doblin, 1991). Indeed, these experiences are often rated in the same top-five life events, as the birth of a child or the loss of a loved one (Griffiths et al., 2016; Griffiths et al., 2006). A key characteristic of the psychedelically induced mystical state, is that this experience is deemed *ineffable*, i.e., difficult to put into words, because it escapes our ordinary concepts and language (Yaden et al., 2016). As such, the experience can only be approximated by using metaphorical language or it needs to be experienced from a first person perspective in order to truly understand what is meant by a mystical experience (Forman, 1990). At the same time, many people indicate that the experience also yields specific *insights*, i.e., people learn something new about themselves and the world, and therefore the experience is considered to have a noetic quality – although, paradoxically such insights are sometimes impossible to put into words and are therefore better characterized as an experience of something that is described as feeling somehow more "real" than ordinary awareness (Yaden et al., 2017a,b). The mystical characteristics of the psychedelic experience could explain their therapeutic potential because the experience provides the person with a different perspective on their life, thereby enhancing the perceived meaning and purpose (Griffiths et al., 2006). However, the mystical experience is a multi-dimensional construct, and it may contain multiple cognitive and affective processes as well as beliefs and attributions, making it more of an umbrella construct than a highly specific mental state (i.e., many of the more specific constructs described below are contained in the mystical experience construct). In addition, more conceptual clarity is needed to foster research on mystical-type experiences and to counter stereotypical and incorrect ideas about mysticism as something that is inherently unscientific (Breeksema and van Elk, 2021).

Relatedly, at higher doses psychedelics can also occasion the experience of *ego-dissolution*, which is characterized by a complete loss of self-awareness (Letheby and Gerrans, 2017). During an experience of ego-dissolution there is a complete absence of self-reflective thought, the experience of an 'I' as being distinct from the world, and of the sense of having a bodily self or a narrative/reflective self. To assess this experience, the ego-dissolution inventory has been developed, which contains items like 'I experienced a dissolution of my 'self' or ego'; 'I felt at one with the universe'; 'I experienced a disintegration of my 'self' or ego' (Nour et al., 2016). At a neural level the experience of ego dissolution has been related to an increased global connectivity between high-level association areas and the thalamus (Tagliazucchi et al., 2016), a reduced alpha power in the posterior cingulate cortex (Muthukumaraswamy et al., 2013), and with a decreased activation of the default mode network (Carhart-Harris et al., 2016). Based on these findings it has been suggested ego dissolution reflects the loosening of priors at a high level in the cortical hierarchy that is involved in instantiating a self-model

that in our ordinary waking consciousness provides a sense of coherence and continuity to our experiences (Letheby and Gerrans, 2017).

A related psychological construct to characterize the subjective effects of psychedelics is the emotion of awe. *Awe* is elicited by the perception of vastness and results in a need to mentally accommodate the experience into one's schemas (Keltner and Haidt, 2003). A multidimensional measure of awe, the Awe Experience Scale (AWE-S; Yaden et al., 2019) includes six sub-scales, including (1) the perception of vastness, (2) the need for accommodation, (3) altered sense of time, (4) feelings of self-loss, (5) feelings of connectedness, and (6) physiological changes (e.g., eyes slightly widening, jaw loosening, chills). The overwhelming nature of the psychedelic experience and the awe-inducing characteristics, could perhaps result in a revision of one's current mental schemes thereby potentially helping people to overcome personal obstacles and problems (Hendricks, 2018).

A driving factor underlying the experience of awe are the sensory effects that are induced under the influence of psychedelics, such as an increase in synesthetic experiences (Terhune et al., 2016), as well as time dilation and visual effects (both with eyes closed and eyes open; Siegel and Jarvik, 1975).

In previous studies it has been found that awe-experiences in response to vast natural scenes are characterized by a similar decrease of the DMN (van Elk et al., 2019) as has been observed for psychedelic experiences (Carhart-Harris et al., 2012; Carhart-Harris et al., 2016), suggesting some potentially similar underlying mechanisms. Psilocybin microdosing also enhanced feelings of awe (van Elk et al., 2021) and participants perceived their body to be smaller during the experience of awe (van Elk et al., 2016). Taken together, these findings fit well with the proposal that awe could be a putative mechanism underlying the psychedelic experience, as proposed by Hendricks (2018).

However, because of the strong overlap between mystical experiences, ego dissolution, and feelings of awe it is often difficult to empirically disentangle these concepts (Taves, 2020). In addition, as-of-yet in the literature there seems to be a one-sided emphasis on positive awe-experiences, while threatening awe (e.g., as can be felt when confronted with natural disasters) – which may be induced by psychedelics as well – has been relatively understudied (Gordon et al., 2017). Finally, whereas most research on the awe-experience has used natural inducers of awe (e.g., vast natural scenes), it remains to be determined how psychedelic-induced awe quantitatively and qualitatively compares to nature-induced awe experiences.

Next to awe, people typically experience a wide variety of emotions during psychedelic experiences. Psychedelic experiences in clinical settings are rated as involving strong positive emotions, but some negative emotions as well (Griffiths, 2006). Aldous Huxley already suggested that psychedelics act as a non-selective amplifier and psychedelics have indeed been shown to increase both conscious and unconscious emotional states and can bring hidden thoughts and cognitions to the surface, which can have an intense emotional valence (Hartogsohn, 2018). In a supportive therapeutic context, the enhanced experience of emotions can facilitate what has been called an emotional breakthrough, which is correlated with beneficial outcomes (Roseman et al., 2019).

As noted above, the acute subjective effects of psychedelics were characterized as a psychotomimetic (mimicking psychosis) through a period of history (Nichols and Walter, 2021). While there appear to be some subjective similarities between psychedelics and psychosis – especially related to the experience of hallucinations, delusions, and/or derealization (Vollenweider et al., 1998) – there appears to be important differences. In particular, the acute subjective effects of psychedelics are transient (lasting around 6 h) and appear to be challenging, yet usually overall positive and meaningful with persisting positive effects (Carhart-Harris et al., 2016; Carhart-Harris et al., 2021; Davis et al., 2021; Griffiths et al., 2016, 2011, 2006). These findings stand in stark contrast to psychosis, which tends to last for days/weeks, is mostly negative, and has largely detrimental effects (Johnson et al., 2019).

While public messaging around psychedelics was overly negative in valence and alarmist for several decades, in the recent literature on psychedelics there seems to be an emphasis on the positive aspects of the psychedelic experience, such as feelings of awe, connectedness and prosociality. Psychological risks are no doubt substantially reduced in clinical settings, but it is important that such risks remain part of the larger discourse regarding psychedelics (Yaden, Yaden, & Griffiths). For example, some studies have adverse psychological consequences such as the potential induction of false memories (Doss et al., 2018) and persisting negative emotions and other challenging psychological content (Carbonaro et al., 2016) are relatively understudied.

The recently developed Challenging Experiences Questionnaire aims to capture the effects that could occur during a bad trip, such as panic attacks, confusion, the feeling of losing one's mind and bodily discomfort (Barrett et al., 2017). Precipitating factors for a bad trip are for instance a high score on the personality trait of neuroticism, a propensity for mood swings and taking a high (compared to a moderate) dose of psychedelics, as this is accompanied by a stronger feeling of losing control. At the same time, the risk of a bad trip in scientific and clinical studies, which are typically conducted in a safe and supportive environment is relatively low (Carbonaro et al., 2016). Also, a bad trip typically does not last the entire duration of the psychedelic experience, but only for a limited amount of time and there have been no reports of persisting adverse effects (Andersen et al., 2021). Moreover, it has even been found that negative and challenging experiences during psychedelics can ultimately have a positive outcome, as it may have helped people in the longer-term to come to terms with specific personal issues (Carbonaro et al., 2016). Lastly, in a clinical trial with psilocybin, it was found that positive emotions were increased and negative emotions decreased for at least a month after drug administration (Barrett et al., 2020).

4.2. Cognition

As we already saw in Section 3.1 psychedelics tend to impair attention and cognitive control; however, psychedelics have also been suggested to enhance psychological and cognitive flexibility.

Several studies have shown that psychedelics can increase *psychological flexibility*, which can be defined as the adaptive response that people can employ to different stressors to promote value-driven action (Davis et al., 2020). It has been found that psychological flexibility mediated the effects of psychedelic-induced experiences and decreases in anxiety and depression. Another study found that psychedelic-assisted psychotherapy increased cognitive flexibility (as measured using perseverative errors in a task-switching paradigm) and psychological flexibility for up to 4 weeks after treatment (Davis et al., 2020), although the increase was not related to symptom improvement.

Cognitive flexibility is a more basic and domain general ability to adaptively switch between various cognitive operations (Uddin, 2021). A psilocybin study (Doss et al., 2021) showed that cognitive flexibility was increased from baseline, as measured by the Penn Conditional Exclusion Test (PCET; Kurtz, 2004). The PCET involves indicating which of four images does not match the others according to a changing set of criteria, testing participants' capacity to quickly adapt to the new criteria with minimal errors. Fewer errors across the changes in this task are understood to indicate more cognitive flexibility. The Doss et al. (2021) study showed an increase in cognitive flexibility following psilocybin administration that persisted for 4 weeks, but the increase in cognitive flexibility was not correlated with previously reported decreases in depression using this sample (Davis et al., 2021).

Psychedelic-induced changes in cognitive and psychological flexibility could potentially explain the trans-diagnostic effects of psychedelics, as impairments in cognitive and psychological flexibility have been related to a variety of disorders, including depression (Stange et al., 2017) and substance abuse disorders (Verdejo-Garcia et al., 2015). We note however, that some studies have also shown that psychedelics can

acutely impair cognitive flexibility (Pokorny et al., 2020), pointing out the need to distinguish between the acute and the post-acute effects of psychedelics on psychological functioning.

In research conducted in the 1960's, there was a strong interest in the question whether psychedelics – due to their strong associative and flexibility-enhancing effects – could enhance *creativity* and problem solving. For instance, at the International Foundation for Advanced Study (IFAS) it was investigated whether mescaline and LSD could help scientists, architects, and artists to find a solution for a specific problem they were struggling with in their practice. The study found that psychedelics indeed helped them to visualize their problems and to come up with more out-of-the-box solutions, although results from this study should be considered preliminary (Harman et al., 1966). Several recent studies have also shown, using standard measures of creativity such as the alternative uses task and the remote associates task, that ayahuasca and psilocybin microdosing resulted in more original and fluent answers (Kuypers et al., 2016). (Kuypers et al., 2016; Prochazkova et al., 2018). However, these tasks are low in ecological validity and synthesizing the results from all different studies there is no clear evidence that psychedelics truly enhance creative thinking (Baggott, 2015; Girn et al., 2020). The lack of consistent effects could be related to the fact that psychedelics might increase associative thinking, while at the same time impairing the ability to select the best alternative from all the different associations that are activated.

Next to enhancing associative thinking, psychedelic substances – when administered in the right set and setting – can also increase *mindfulness* and being present in the here-and-now. There exists a synergistic relationship between psychedelics and meditation: prior experience with meditation can help people to navigate their psychedelic experience (Payne et al., 2021), while the use of psychedelics can also trigger and facilitate meditative depth (Soler et al., 2016). A psilocybin study found that a condition that received instruction in meditation and psilocybin had more benefit than conditions receiving psilocybin alone or meditation instructions alone (Griffiths et al., 2018). In a 5-day meditation retreat study, the administration of psilocybin to mindfulness practitioners resulted in a strong experience of ego-dissolution and a subsequent deepening of the meditative practices than those who did not receive psilocybin (Smigielski et al., 2019). In a cross-sectional study, prior psychedelic use was found to be strongly associated with engaging in mindfulness practices, and both practices were associated with improved well-being (Qiu and Minda, 2022).

The capacity of psychedelics to enhance mindfulness may suggest a commonality at a deeper level, as both psychedelics and mindfulness meditation have been characterized to be "mind-revealing experiences" (Lyon, 2022). The word 'psychedelic' literally means 'making the mind visible' and was famously coined in an exchange between the writer Aldous Huxley and the psychiatrist Humphrey Osmond. Mindfulness meditation – through the lens of predictive processing - has also been characterized as a deconstructive process, whereby increased stages of meditative depth are associated with a stronger reduction of abstract and conceptual processing (Laukkonen and Slagter, 2021). According to some, both psychedelics and mindfulness meditation could perhaps complement one another (e.g., Letheby, 2021). According to others, they could even fulfill complementary roles in clinical practice, metaphorically speaking as compass (i.e., psychedelics provide direction) and vehicle (i.e., meditation helps one to integrate and deepen the insights gained through psychedelics; cf., Payne et al., 2021).

4.3. Beliefs

Psychedelic experiences can trigger attributions of supernatural encounters and increase suggestibility, resulting in changes in metaphysical beliefs, worldviews, and the perception of enhanced feelings of meaning. Many people have vivid encounters with seemingly (to some) supernatural entities and other-worldly realities during their psychedelic experiences. Under the influence of psychedelics, participants can report God encounters, which have a similar impact as God experiences that occurred spontaneously without the use of psychedelics. (Griffiths et al., 2019; Yaden et al., 2017a,b). The context in which psychedelics are used appears to influence the entities that people experienced. It has been found, for instance, that DMT administered in a hospital setting primarily resulted seeing of aliens performing surgery (Strassman, 2000). DMT and the Amazonian brew ayahuasca (which includes DMT) appear to have a high likelihood to occasion encounters with spiritual entities and to facilitate experiences of two-way communication that are perceived to be telepathic (Strassman, 2000).

A concern is that psychedelics, rather than helping people to deal with their psychological problems, may actually result in 'spiritual bypassing', whereby problems are interpreted in a spiritual or religious framework (e.g., being caused by demons or evil spirits; cf., Trichter, 2010), or they even can foster 'grandiosity' and narcissism as the person may attribute special significance and social status from the revelations that he received. In order to mitigate these issues, a careful approach to psychedelic therapy and research is necessary that involves the crafting of 'psychedelic apprenticeship' may be called for (Timmermann et al., 2020). This involves empathic resonance and intersubjective validation and mediation with the participant / patient within the broader community, through applying know-how and, for example, the 'accept, connect and embody' model of psychedelic-assisted psychotherapy (Watts and Luoma, 2020). Lastly, it is important that religious/spiritual interpretations are not pushed onto participants or patients in research or clinical settings by therapists or session monitors (Johnson, 2021; Yaden et al., 2022).

Experimental research has shown that the use of psychedelics can also result in lasting changes in one's personal beliefs and can increase one's belief in dualism (i.e., seeing body and mind as two separate entities) and in afterlife beliefs (Timmermann et al., 2020). In a recent study it was found that following a psychedelic retreat, participants showed a change in their metaphysical beliefs, moving from a physicalists or materialist to a more panpsychistic worldview (Timmermann et al., 2021). A large-scale retrospective study has also shown that the DMT experience can have a powerful effect on people's worldview, as more than half of all participants who first considered themselves atheists didn't do so after their DMT experience (Davis et al., 2020). While some scholars (e.g., Taves, 2020) have argued that psychedelic research has monolithically studied mystical experience to the exclusion of other mental states, such reported experiences are in fact being measured and reported in many studies, though their relevance to therapeutic outcomes appears to be limited.

Because of the profound impact that psychedelics can have on people's worldview, it has been suggested that psychedelics can cause an 'ontological shock', resulting in a dramatic revision of one's prior beliefs (Nour et al., 2016). This shock is likely related to the strong noetic quality and the ineffability accompanying the psychedelic experience, driving people to attribute high significance, meaning, and truth to the insights they obtained. This raises additional challenges for psychedelic research and therapy, as it remains an open question whether, as a by-product of psychedelic therapy, people might become more spiritual. Substantial attention is being paid to the issue of belief change in terms of informed consent (Smith and Sisti, 2020), as well as recommending a metaphysically agnostic approach in the research and clinical contexts (Nayak and Griffiths, 2022).

Next to their effects on worldviews and beliefs, it has also been found that LSD acutely increases suggestibility as measured using the creative imagination scale (Carhart-Harris et al., 2015). In addition, the strong prior expectations that many people have about psychedelics directly contribute to the psychedelic experience and as a consequence it has been suggested that psychedelics may act as a 'super-placebo' (Hartogsohn, 2016). Specifically, strong prior expectations (e.g., that a specific intervention will likely trigger a mystical experience) will increase the likelihood of having e.g., a mystical-type experience (Maij et al., 2019), and this placebo-effect is further boosted by the psychedelic-induced

suggestibility. Given this strong entanglement of prior beliefs, suggestibility, and set and setting, it has been suggested that psychedelics amplify a meaning-making response, resulting in a prolonged and enhanced perception of meaning and significance (Hartogsohn, 2016, 2018).

4.4. Social connection

Psychedelics exert strong social effects, including feelings of connectedness, communitas, and empathy. Classic psychedelics often induce strong feelings of connectedness with other people, with nature and with humanity and the universe as a whole (Carhart-Harris et al., 2018). Feelings of connectedness and unity are measured in the mystical sub-scale of the mystical experience questionnaire (MEQ; Barrett et al., 2015), the oceanic boundlessness sub-scale of the five dimensional altered states of consciousness scale (5D-ASC; Dittrich, 1998), the ego dissolution inventory (EDI; Nour et al., 2016), the non-dual awareness assessment (NADA; Hanley et al., 2018), and the connectedness subscale of the awe experience scale (AWE-S; Yaden et al., 2019). The overlap in these measures can be viewed as problematic (i.e., as "jangle", or different measures measuring the same latent construct) or as a good sign that psychometric convergence is occurring across the field. In any case, additional factor analytic and network analysis studies are warranted to make progress on more precisely specifying the acute subjective effects of psychedelics regarding connectedness (and more generally).

Feeling connected to others also contributes to the experience of more meaning and facilitates a more conscious way of living, which can be reflected in a more environmentally aware lifestyle following a psychedelic experience or retreat (Forstmann and Sagioglou, 2017). Feelings of connectedness could also contribute to the relief from depression and death anxiety, as the experience directly challenges one's prior maladaptive beliefs about oneself (Forstmann et al., 2020). Extreme cases of connectedness may be experienced during the feeling of ego-dissolution, which may involve both an enhanced of belonging and a loss of one's fears and concerns (Yaden et al., 2017b). These experiences might also have an effect on one's personality, such as observed in the effects of psychedelics on narcissistic personality traits (van Mulukom et al., 2020).

While most social and cultural dynamics are beyond the scope of our review, we note that psychedelics are frequently used in structured social contexts. Such contexts, which include traditional and contemporary group ritual settings, can impact the outcomes of psychedelic use. Anthropologist Victor Turner labeled such group ritual contexts communitas, which he described with an emphasis on their temporary flattening of social hierarchies and enhanced social cohesion. An observational, web-based study of psychedelic ceremonies found that scores on a measure of group cohesion called the Communitas Scale predicted outcomes measured 4 weeks after the experience such as well-being and social connectedness (Kettner et al., 2021).

In addition to feelings of social connection, empathy might be impacted by psychedelics. Empathy has been variously defined, sometimes in ways that emphasize feeling what others feel and sometimes as a compassionate concern for others (Bloom, 2017; Hojat et al., 2001; Singer and Klimecki, 2014). The multifaceted empathy test (MET) is one common measure of empathy. Pokorny et al. (2017) found that psilocybin acutely increased the MET a few hours after administration. Mason et al. (2019) found that MET scores were increased for 7 days following psilocybin administration in a retreat setting. Dolder et al. (2016) compared a lower and higher dose of LSD and found that MET scores were higher in the higher dose condition. An online retrospective survey study found that decreases in narcissism as well as increases in empathy were reported after psychedelic experiences (van Mulukom et al., 2020).

4.5. Behavior

Finally, following on the observed psychedelic-induced increase in neuroplasticity, it has been suggested that psychedelics offer a therapeutic window of opportunity for learning new healthy habits and behavior change. Combined with behavior change programs, such as cognitive behavioral therapy, psychedelics might offer a strong potential for fostering a healthier lifestyle, including improved diet, physical exercise, and mindfulness practices (Teixeira et al., 2022). These behavioral effects can also be directly triggered by the psychedelic experience, as it has been shown for instance that psychedelics increase nature-relatedness (Lyons and Carhart-Harris, 2018) and can facilitate a more pro-environmental attitude (Forstmann and Sagioglou, 2017).

Although there is no systematic research on psychedelic-induced changes in habits and behavior, a review of the available cross-sectional and clinical studies indicates anecdotal evidence for a healthier lifestyle (e.g., less alcohol consumption, smoking cessation, healthier diet) to be associated with the use of psychedelics (Teixeira et al., 2022). Several clinical trials with psilocybin have found self-reported positive changes to behavior (Griffiths et al., 2016, 2018, 2011, 2006). As such, psychedelic-assisted psychotherapy and psychedelic interventions also appear to offer a strong potential for the treatment of substance-abuse disorders, eating disorders, and for preventive healthcare for 'lifestyle diseases'.

Limitations: Despite the profound acute effects of psychedelics on subjective experience, most of the effects described in this section rely on self-report measures and as such are prone to socially desirable responding, demand effects, and suggestibility. Specifically, due to the psychedelic-induced enhancement of suggestibility (Carhart-Harris et al., 2015) and the strong prior beliefs about psychedelics (Hartogsohn, 2018), participants might have a general motivated tendency to over-report the subjective effects associated with their psychedelic experience.

Recent studies have shown that even when taking inert placebo-psychedelics, some participants report the same subjective effects, as when given a full dose of psilocybin (Olson et al., 2020). Specifically, participants scoring high on the personality trait of absorption may be prone to suggestibility effects (Lifshitz et al., 2019) and high absorption participants also tend to report the strongest subjective effects under psychedelics (Bouso et al., 2018). Thus, taking these personality measures into account, and relating them to the underlying neurobiological pathways, is an important challenge for future psychedelic research.

Summary In this section, we highlighted the different psychological explanations that have been offered for the therapeutic efficacy of psychedelics, including altered and affective states, changes in cognition, belief change, social effects and behavior change. In practice, these experiences are often interrelated and share similar characteristics. As such a network-based approach (Borsboom and Cramer, 2013) as applied to the 5D-ASC scale (Studerus et al., 2010), as well as the others mentioned above, may be a fruitful way to highlight how the different characteristics of the psychedelic experience are interrelated.

5. Relationship between the different levels of analysis

In the current literature we see two different views regarding the relationship between the different levels of analysis that we discussed in this paper: one is *the integration view*, which would describe how, ultimately, the different levels all converge on a similar causal mechanism (while leaving open the question whether the different levels ultimately can be entirely reduced to one another). The other is *the pluralistic view*, which would argue for the notion of pluralistic causation, meaning that ultimately integration between different levels of analysis is not possible. Below we discuss both possibilities in terms of their merits and pitfalls.

5.1. The integration view

The observation that psychedelics can be helpful in the treatment of depression, anxiety, addiction, and obsessive-compulsive disorder, may suggest a common pathway underlying these different biomedical disorders. This raises the question what theories can account for this potentially trans-diagnostic efficacy of psychedelics. At least one theory has been advanced that attempts to integrate the various levels of analysis reviewed above.

In psychopathology, the quest for a common factor underlying different forms of mental illness has suggested that the so-called p-factor (Caspi et al., 2014), which captures a general hallmark of psychopathology. Although different interpretations have been provided for the functional significance of this factor (Carver et al., 2017), a recurring feature of psychopathology seems to be a tendency for a rigid and persistent vs. a more associative and flexible processing style. Healthy cognitive and mental functioning requires the adaptive switching between these two processing styles through a process of meta-control (Hommel and Colzato, 2017), but this ability may be impaired in psychopathological disorders, such as depression, addiction, or post-traumatic stress-disorder.

The primary mechanism of action of psychedelic-assisted psychotherapy may thus be the breaking of rigidity by introducing enhanced meta-control, which results in a therapeutic window of opportunity characterized by a more flexible and open processing style. Indeed, the construct of psychological flexibility from the Acceptance and Commitment Therapy (ACT) framework has been shown to be enhanced by psychedelics (Davis et al., 2020). At the neurocognitive level, according to the REBUS and the CCC model, there is a destabilizing of existing networks, a loosening of maladaptive priors and an increased sensitivity to bottom-up prediction error signaling. Enhanced cognitive flexibility from psilocybin has been observed using a well-validated cognitive task (Doss et al., 2021). At the pharmacological level, these neurocognitive mechanisms are mediated by serotonergic, dopaminergic and glutamergic activity, which can affect the precision by which predictions and beliefs are coded (Sterzer et al., 2018). The increase in glutamate and BDNF in turn, also induces neurogenesis enabling the formation of new connections in the brain.

On this integrative account, different types of psychedelic-assisted psychotherapies also act at different explanatory levels. A distinction can be made between *psycholytic therapy*, whereby a low dose of psychedelics is repeatedly used as a way to facilitate the psychotherapeutic process, and *psychedelic therapy* in which a large dose is used to induce an intense and transformative experience (Majić et al., 2015). Whereas psycholytic therapy may primarily act at a pharmacological and neurocognitive level, psychedelic therapy mainly targets the psychological level by inducing a specific psychological experience. A third treatment approach can also be distinguished that is primarily focused on the working mechanisms of psychedelics at a pharmacological level. Examples of this approach may be found in microdosing with LSD or psilocybin (Kuypers et al., 2019), ketamine-infusions for the help of treatment-resistant depression (Fond et al., 2014), and the recent trend to use psychoplastogens (Olson, 2018). Future research will need to establish the efficacy and applicability of these three approaches for a variety of different psychological and biomedical disorders, thereby casting more light on the relative importance of the different levels of analysis in accounting for the therapeutic effects of psychedelics.

A robust integrative account, regardless of whether a predictive processing or flexibility-based account ends up receiving the most empirical support, has the virtue of bridging levels of analysis that have proven difficult to bring together in any subject in the psychological and brain sciences. Psychedelics provide a well-characterized and singular chemical trigger (in contrast to many other topics in psychology in which the relevant stimuli are typically more complex). Additionally, psychedelic research is already occurring on psychological, neurocognitive, and pharmacological levels, providing the opportunity for explanations that span multiple levels of analysis.

5.2. Pluralistic causation

While the previous section briefly described attempts to integrate some of the findings at various levels of analysis that we have reviewed – and we support efforts to discover a comprehensive theory of how psychedelics exert their effects – it is also possible that no such theory is possible. As we already highlighted when reviewing the empirical evidence, many existing theories regarding the pharmacological, psychological, and neurocognitive mechanisms underlying psychedelics are currently underdetermined by the data and suffer from several methodological and conceptual shortcomings (see also below). Thus, we should be cautious when attempting to integrate the insights from these different strands of evidence (in addition to awaiting more independent confirmatory replication studies to establish the robustness of the effects). However, at a theoretical level there are also reasons to believe that, instead of grand unifying theories, the field may need to look to pluralistic models of causation when considering psychedelics and their effects.

Pluralistic theories of causation postulate that multiple complementary pathways are necessary in order to adequately describe a given phenomenon (Johnson et al., 2019). Pluralistic theories are common in psychiatry and the psychological sciences. A parallel may be drawn with other mental phenomena that require a pluralistic theory of causation, such as mental illness in psychiatry. According to, despite extensive and on-going research into mental illness, different levels of analysis—such as the genetic, neurological, psychological, and social—have yet to be coherently integrated (or reduced) into a single explanatory theory. Instead, as illustrated in the DSM's "bio-psycho-social" framework, these are treated as clearly inter-related and highly correlated yet unintegrated levels of explanation. A similar sentiment can be found in 'holistic' approaches to psychopathology (Stanghellini and Rossi, 2014) and in so-called 4E approaches to cognition, where the 4Es stand for the embodied, embedded, extended and enactive nature of the human mind (Newen et al., 2018).

Similarly, it may be that the effects of psychedelics are too psychologically and socially situated for a single theory to prove satisfactory. On this account, ultimately, the psychedelic experience cannot be reduced to a single cause, but it is rather the interplay of multiple causal pathways within and between the different levels that accounts for both the short- and the long-term effects that psychedelics induce. In line with proposed bio-psycho-social and 4E models, additional levels of analysis, including social, cultural, and historical factors would need to be included in such a pluralistic account as well (de Haan, 2021). As outlined in this paper, establishing these pathways requires converging lines of evidence to establish causation (e.g., manipulating the working of the 5-HT_{2A} receptor; correlating subjective experiences to brain states, etc.).

Recently, a similar call for explanatory pluralism to account for the effects of psychedelics has been proposed (Aftab and Stein, 2022) and an implication of this view is that no single universal mechanism might account for the therapeutic efficacy of psychedelics. That is, psychedelics could have beneficial effects on depression by increasing neuroplasticity for one patient, while for another patient the improvement might be due to the psychedelic-induced mystical experience. Therefore, a pluralistic account calls for the importance of customized medicine instead of a one-size-fits-all approach. Personalized network approaches in psychedelic-assisted psychotherapy potentially allow more well-informed and targeted interventions, e.g., by highlighting the cluster of neurobiological or psychological symptoms that could be targeted (Lewis-Healey et al., 2022).

6. Looking ahead: An agenda for psychedelic research

However, we believe there is reason to hold out hope for a

parsimonious and far-reaching theory for the effects of psychedelics that stretches across levels of analysis. While psychedelics involve a number of psychological and social factors, the coherence of the trigger (i.e., the fact that it is a particular, well-characterized molecule) separates it from many much vaguer and more multi-dimensional psychological topics, as we have discussed. This overall aim underscores the importance of using an interdisciplinary approach to study the mechanisms underlying the psychedelic experience and the potential beneficial therapeutic outcomes that they yield.

Understanding the relative contribution of the different explanatory levels to the therapeutic effects observed with psychedelics is important in order to provide an adequate scientific understanding of psychedelic experiences, which could also potentially contribute to a more targeted therapeutic approach. For instance, it could be that other methods to occasion mystical-like experiences (e.g., through practices like holotropic breathwork or meditation) are also effective in fostering a sense of meaning and enhancing overall well-being (Yaden et al., 2017b). Comparative studies directly contrasting the efficacy of different therapeutic practices (e.g., psychedelics, breathwork exercises, mindfulness meditation) could eventually shed light on the question whether psychedelically occasioned mystical experiences are unique in the effects they exert. It is also possible that various synergistic approaches are needed whereby psychedelic therapy is complemented with various practices such as meditation or breathing exercises (Smigielski et al., 2019).

An alternative research approach could be to target the specific effects of psychedelics at a pharmacological and / or neurocognitive level, without the accompanying psychological experiences, for instance by treating patients with a combination of psychedelics and ketanserin (Preller et al., 2017), psychedelics without the psychoactive component (for a debate see Olson, 2020; Yaden & Griffiths), or by administering psychedelics to vegetative state patients (Scott and Carhart-Harris, 2019). That way it can be established whether the pharmacological changes induced through psychedelics also have an effect at the psychological level.

At the same time, we should keep in mind that the psychedelic state is a complex and multifaceted experience that is characterized by a wide variety of different features and characteristics (Breeksema and van Elk, 2021). Additionally, the acute subjective effects of psychedelics are dynamic and different characteristics may become more or less prevalent during different phases of the psychedelic state. Each of these characteristics, in turn, could perhaps be accounted for by different pharmacological, neurocognitive, and psychological mechanisms that are outlined above.

In order to do justice to the dynamic nature of the psychedelic experience, we need more refined measurement instruments, as can be found for instance in the microphenomenological approach (Petitmengin et al., 2019). This approach aims to provide an in-depth assessment of different stages and aspects of an experience, through a carefully crafted interviewing method. This method has been successfully applied, for instance, to account for the complex phenomenology accompanying mindfulness meditation experiences, e.g., in relation to the becoming aware of a thought (Petitmengin et al., 2019). Another recent trend is to focus on the differential functions of resting state networks (Diaz et al., 2013), which allows to couple dynamic changes in brain activity (e.g., increase or decrease of the DMN) to accompanying changes in subjective experience. When carefully combined, these methods may allow for more in-depth insight in the complex and multifaceted character of the psychedelic experience.

Finally, a word of caution, as many of the findings presented in this review are still preliminary. The field of psychedelic research is still in its infancy and so far much of the field has not jumped on the bandwagon of using open science practices (Petranker et al., 2020). This is problematic, as there is a potential of researcher bias, especially because many people doing research in this field are psychedelic enthusiasts. This introduces the potential confound of motivated reasoning, confirmation bias and a selective focus on positive effects induced by psychedelics, which could lead to overly enthusiastic representations of their effects (Yaden et al., 2021). Many published studies are underpowered and given the relatively high degrees of freedom in data analytic choices, it is not always clear to what extent theoretically important effects (e.g., the entropic brain hypothesis) are actually supported by empirical data (e.g., regressing out the global signal in fMRI can drastically alter the patterns of connectivity observed; cf., Preller et al., 2018).

Lastly, psychedelic substances are difficult to blind effectively due to their dramatic subjective effects (Aday et al., 2022).

Fortunately, there is a remedy for these concerns, as within mainstream psychology and neuroscience research many steps have been taken to improve scientific practices, including the use of preregistration, open materials, open data, registered reports, multiverse-analyses, multi-analyst approaches, and adversarial collaborations (Chambers et al., 2015). These initiatives increase the transparency of research, offer the possibility of sharing of materials between research labs, allow independent replication attempts, and allow to more clearly distinguish between exploratory and confirmatory hypotheses. Hopefully these initiatives will soon be implemented in psychedelic research as well in order to increase the credibility of this important research field.

7. Conclusion

Classic psychedelics, such as LSD and psilocybin, induce a wide range of different effects at the pharmacological, the neurocognitive, and the psychological level. The critical review of the mechanisms provided in this paper may ultimately reflect different sides of the same coin, as exemplified in the REBUS model for instance, that accounts for psychedelics' effects at different levels of analysis. At the same time, to fully account for the multifaceted and dynamic nature of the psychedelic experience, new methodological developments and a pluralistic theory of causation may be needed. Combined with a research agenda for open science and replicability, ultimately this approach may provide a starting point for a more robust understanding of psychedelics.

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